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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
WINKLER, ULRIKE	
ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 11/06/2002 10

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/744,659	CHEVALIER, MICHEL	
	Examiner	Art Unit	
	Ulrike Winkler, Ph.D.	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Peri d for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 July 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *11-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *6* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant's election with traverse of Group I in Paper No. 9 is acknowledged. Upon review and reconsideration in view of applicant argument the prior Election/Restriction requirement is withdrawn. Claims 11-19 are under consideration in the instant office action.

The requirement is still deemed proper and is therefore made FINAL.

Specification

Applicant is required to update the status (pending, allowed, ect.) of all parent priority applications in the first line of the specification.

This application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is required.

This application does not contain a separate section of a brief description of the figure. Although the figure is described on page 18, lines 21-35, a separate section containing a brief description of the figure is required.

The following guidelines illustrate the preferred layout for the specification of a utility application. These guidelines are suggested for the applicant's use.

Arrangement of the Specification

As provided in 37 CFR 1.77(b), the specification of a utility application should include the following sections in order. Each of the lettered items should appear in upper case, without underlining or bold type, as a section heading. If no text follows the section heading, the phrase "Not Applicable" should follow the section heading:

(a) TITLE OF THE INVENTION.
(b) CROSS-REFERENCE TO RELATED APPLICATIONS.

(c) STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT.
(d) INCORPORATION-BY-REFERENCE OF MATERIAL SUBMITTED ON A COMPACT DISC (See 37 CFR 1.52(e)(5) and MPEP 608.05. Computer program listings (37 CFR 1.96(c)), "Sequence Listings" (37 CFR 1.821(c)), and tables having more than 50 pages of text are permitted to be submitted on compact discs.) or
REFERENCE TO A "MICROFICHE APPENDIX" (See MPEP § 608.05(a). "Microfiche Appendices" were accepted by the Office until March 1, 2001.)
(e) BACKGROUND OF THE INVENTION.
(1) Field of the Invention.
(2) Description of Related Art including information disclosed under 37 CFR 1.97 and 1.98.
(f) BRIEF SUMMARY OF THE INVENTION.
(g) BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWING(S).
(h) DETAILED DESCRIPTION OF THE INVENTION.
(i) CLAIM OR CLAIMS (commencing on a separate sheet).
(j) ABSTRACT OF THE DISCLOSURE (commencing on a separate sheet).
(k) SEQUENCE LISTING (See MPEP § 2424 and 37 CFR 1.821-1.825. A "Sequence Listing" is required on paper if the application discloses a nucleotide or amino acid sequence as defined in 37 CFR 1.821(a) and if the required "Sequence Listing" is not submitted as an electronic document on compact disc).

Information Disclosure Statement

An initialed and dated copy of Applicant's IDS form 1449, Paper No. 6, is attached to the instant Office Action.

The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Drawings

The drawings have been approved by the Draftsperson.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 11-19 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The instant invention does not provide a sufficient written description regarding a composition comprising a naturally-occurring HIV pg160 that comprises the attributes of: (1) binding to CD4, (2) binds to an anti-gp120 antibody capable of neutralizing HIV infection of cells *in vitro*; (3) binds to an anti-gp41 antibody; and (4) has no inter-chain disulfide bridges. The prior art indicates that recombinantly produced gp160 forms oligomers which are stabilized by intermolecular disulfide bonds and or non-covalent interactions (et Hallenberger et al., Virology, 1993, see figure 2 c and d). The formation of the inter-chain disulfide bonds appear to be necessary to stabilize the oligoemeric form corresponding to dimmers, trimers and tetramers (see Hallenberger et al., page 511, paragraph, 2). Neither the specification nor the prior art provide a sufficient written description that would let the ordinary artisan to conclude that there are naturally-occurring gp160 timers that are not stabilized by inter-

chain disulfide bonding. Therefore, there is insufficient written description for a naturally-occurring gp160 that contains no inter-chain disulfide bonds.

Furthermore, Claims 18 and 19 make reference to the expression of gp160 or fragment thereof. The only gp160 fragment disclosed in the specification is a gp160 in which the transmembrane region has been deleted (see specification page 16, line 24 to page 17, line 7). The specification does not provide a description of what portions of gp160 is required to from a trimer without any inter-chain disulfide bonds. Therefore, there is insufficient written description for fragments of gp160 that form trimers, are able to bind CD4, bind antibodies to gp120, bind antibodies to gp41 and that additionally posses no inter-chain disulfide bonds.

Claims 11-19 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Instant claims are evaluated for scope of enablement based on the Wands analysis. Many of the factors regarding undue experimentation have been summarized in *In re Wands*, 858 F.2d 731,8 USPQ2d 1400 (Fed.Circ.1988) as follows: (1) the nature of the invention, (2) the state of the prior art, (3) the predictability or lack thereof in the art, (4) the amount of direction or guidance present, (5) the presence or absence of working examples, (6) the quantity of experimentation necessary, (7) the relative skill of those in the art, and (8) the breadth of the claims. The Wands factor analysis, such an analysis does not need to be specifically enumerate (points 1-8) but only needs to have a select few of the factors present discussed in a rejection. In

order to show applicant that the appropriate factors have been taken into account, an enumerated Wands analysis follows.

The instant invention is drawn to a composition comprising a purified gp160 trimer. The example disclosed on page 18 lines 1-20 comprises the following steps: the gp160 is expressed from a vaccinia vector the glycoprotein is purified using successive column chromatographic methods. The 3.5×10^{-9} moles of the resulting product, which contains dimers, trimers and tertramers (see Hallenberger et al. Virology 1993, figure 2c) are then reduced with 4.86×10^{-6} moles of DTT (containing two reactive sulfhydral groups) for 15 seconds, followed by blocking of the sulfhydral groups with 9.5×10^{-6} moles N-ethylmaleimide which is added directly into the mixture without the removal of the reducing agent, this reaction is incubated for 15 min before the reoxidation step with reduced glutathione. SDS is added to the resulting mixture and the mixture is then dialyzed resulting in gp160 which is "exclusively in the form of trimers" (page 18, line 20). In reviewing the literature regarding reactions with N-ethylmaleimide (see Smyth et al. Biochemical Journal 1964; Riordan et al. Methods in Enzymology 1972 and Pierce Product Instruction #15150 regarding maleimide chemistry) the following observation are made: the reaction mixture should be kept between pH 6.5-7.5, above this pH the reaction with amine groups becomes more significant. The sulfhydral containing reducing agent needs to be removed before the reaction with N-ethylmaleimide is to proceed, as the reaction with the small thiol containing molecules is more rapid (occurs within 2 min) than with the thiols contained in protein (see Riordan et al. page 454, 1st paragraph). The reaction disclosed in the specification reduces, blocks and reoxidizes allowing the available sulfhydrals to reform disulfide bridges. Therefore, based on the description in the specification one having

ordinary skill in the art could not conclude that applicants have described a product that contains gp160 timers that does not contain any inter-chain disulfide bridges. Therefore, it is not clear how the instantly claimed products differ from the products in the prior art (Hallenberger et al. Virology 1993 or Schwaller U.S.Pat. NO. 6,140,059). The specification has not provided any indication that there are no inter-chain disulfide linkages present in their resulting product and that the resulting product will retain the coiled-coil structure. A showing that there are no inter-chain disulfide bonds present could be achieved by presenting a gel in which the "trimer" would run as a monomer under non-reducing conditions and their EGS cross-linked product would run as a timer under the same conditions. Based on the steps outlined in the specification the ordinary artisan could not conclude that the blocking agent N-ethylmaleimide reacts with the sulfhydral group in the gp160 and does not react with the excess DTT present in the mixture. The order of carrying out the particular steps is also important (claim 18 and 19) comprise steps but do not have a set sequential order that must be followed. Therefore the alkylating agent could be added before the reducing agent this method would not result in the instantly claimed trimer that contains no inter-chain disulfide bonds. Also the specification has not provided any indication that following the steps of reducing and oxidizing (claim 19) will result in the in a trimer that does not contain inter-chain disulfide bonds. The ordinary artisan would expect that after oxidizing the previously reduced sulfur group the sulfur is then capable of forming disulfide bonds and is driven in that direction in order to become more stable. Additionally, the specification has provided no experimental results that indicate the claimed trimer is more reactive with CD4 than the naturally occurring trimer found on the surface of an HIV particle. Therefore, based on what is presented in the specification the ordinary artisan could not conclude

that the instant invention is enabled for a gp160 trimer that does not contain any inter-chain disulfide bonds.

The instant invention is additionally drawn to a vaccine composition (claim 16 and 17) comprising a gp160 trimer protein. The specification does not sufficiently support the claimed vaccine. The term "vaccine" by definition implies any preparation intended for active immunological prophylaxis; e.g., preparations of killed microbes of virulent strains or living microbes of attenuated (variant or mutant) strains; or microbial, fungal, plant, protozoal, or metazoan derivatives or products. Although just about any protein when inoculated can cause an immune reaction, the prophylactic nature of this reaction is not guaranteed and has to be experimentally determined. Prophylaxis is defined as the prevention of disease or of a process that can lead to disease. This is achieved by use of an antigenic (immunogenic) agent to actively stimulate the immunological mechanism, or the administration of chemicals or drugs to members of a community to reduce the number of carriers of a disease and to prevent others contracting the disease. It is well known in the art that retroviral therapies, especially HIV therapies, are refractory to anti-viral therapies (see Fahey et al., Clinical Experimental Immunology, 1992; Letvin, Science, 1998). The obstacles to developing a successful therapy of HIV are well documented in the literature. These obstacles include (a) the extensive genomic diversity and mutation rate associated with the HIV retrovirus, particularly with the respect to the gene encoding the envelope protein. (b) The fact that the mode of viral transmission includes both virus-infected mononuclear cells, which pass the infecting virus to other cells in a covert manner, as well as via free virus transmission. (c) The establishment of a latent viral infection. (d) The ability of the virus to evade the immune responses in the central nervous system due to the

blood-brain barrier. (e) The complexity and variation of the pathology of HIV infection in different individuals. (f) The inability of a natural infection to one strain of HIV to protect an individual from being infected with another strain of HIV (Machuca et al. Intervirology 1999, see discussion). These obstacles establish that the contemporary knowledge in the art would not allow one of skill in the art to use the claimed vaccine to treat and/or prevent HIV infection without undue experimentation. Furthermore, it is well known in the art that individuals infected with HIV produce neutralizing antibodies to the virus, yet these antibodies are not protective and do not prevent the infection from progressing to its lethal conclusion. Applicants have not provided any convincing evidence that their claimed vaccine is indeed useful as a therapeutic or preventative for HIV infection and have not provided sufficient guidance in to allow one skilled in the art to practice the claimed invention without undue experimentation. In the absence of such guidance and evidence, the specification fails to provide an enabling disclosure.

Conclusion

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ulrike Winkler, Ph.D. whose telephone number is 703-308-8294. The examiner can normally be reached M-F, 8:30 am - 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel, can be reached at 703-308-4027.

The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for informal communications use 703-308-4426.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Ulrike Winkler, Ph.D. 11/8/02